IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Bror Morein et al.
Appln. No.	: 10/550,026
Filed	: June 11, 2007
Title	: COMPOSITION COMPRISING ISCOM PARTICLES AND LIVE MICRO-ORGANISMS
Conf. No.	: 6185
TC/A.U.	: 1648
Examiner	: Zachariah Lucas
Customer no.	: 00116
Docket No.:	: ALBI-41848

DECLARATION UNDER 37 CFR 1.132

Sir:

This Declaration under 37 CFR 1.132 is filed in response to the outstanding Office action of January 12, 2010.

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DECLARATION OF BROR MOREIN

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Bror Morein, having knowledge of the facts set forth herein, declares as follows:

1. I presently reside at Ollonstigen 3, Uppsala, Sweden.

2. I am a co-inventor of the subject matter claimed in the above-captioned patent application.

3. My qualifications, publication list, and record as an inventor are already of record based on my previously filed Declaration dated May 18, 2009.

4. I understand that the reference to Morein (U.S. Pat. No. 5,679,354) remains at issue in this case, in part based on the Examiner's concern that a person of ordinary skill could have had a reasonable expectation of success with regard to use of the claimed compositions and methods because the Morein '354 patent indicates that no side effects in the form of local reactions were noted in host mice following immunization with envelope protein from influenza virus in the form of iscom complex particles or with iscom matrix particles and

that a person of ordinary skill could have understood the absence of such side effects to imply that live micro-organisms could likely survive long enough in the hosts to stimulate long-lived specific immunity. With respect to the Examiner's concern, it is my opinion that a person of ordinary skill would not have had a reasonable expectation of success with regard to use of the claimed compositions and methods, even taking into account the disclosures of the Morein '354 patent, because iscom particles administered at dosages similar to those reported in the Morein '354 patent were known to trigger intense inflammatory responses in a host and to be cleared rapidly from sites of injection, side effects in the form of local reactions were known to be most common with adjuvants that are not cleared rapidly from sites of injection, not with adjuvants, such as iscom particles, that are cleared rapidly, and thus an absence of side effects in the form of local reactions would have been understood to reflect rapid clearance of iscom particles from sites of injection, not a lack of intensity of iscom-triggered inflammatory responses.

5. The fact that iscom particles were known to trigger intense inflammatory responses in a host at dosages similar to those reported in the Morein '354 patent is shown, for example, in a reference to Smith, 162 Journal of Immunology 5536, 5536-37 (1999) (hereinafter "Smith I"), which is already of record in this case and which discloses that intraperitoneal injection, in mice, of iscoms at a dosage equivalent to 0.5 µg of Quil A and 5 µg of OVA protein "induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes," and that "[m]any of the recruited cells had phenotypic evidence of activation and secreted a number of inflammatory mediators, including nitric oxide,

reactive oxygen intermediates, IL-1, IL-6, IL-12, and IFN-γ." For comparison, the dosages reported in the Morein '354 patent were 0.1 µg of iscom matrix or 5 µg of iscom including antigen prepared according to EPC 83850273.0. Morein '354 patent, col. 8, lines 37-42. The fact that iscom particles were known to trigger intense inflammatory responses is also shown, for example, in references to Morein, 19 Methods 94, 95-96 (1999), and to Smith, 76 Immunology & Cell Biology 263, 266-67 (1998), which are also submitted herewith.

6. The fact that iscom particles were known to be cleared rapidly from sites of injection is shown for example in a reference to Sjölander, 15 Vaccine 1030, 1031-32, 1035 (1997) (hereinafter "Sjölander I"), which is submitted herewith. Specifically, Sjölander I disclosed that subcutaneous administration of radioactive influenza virus iscoms, i.e. iscoms including solubilized influenza protein, in mice, at dosages equivalent to 3 µg of Quillaja saponins and 3 µg of influenza protein was followed by rapid (< 3 hours) clearance and organ distribution of the influenza virus iscoms, with iscoms being distributed particularly to draining lymph nodes. Sjölander I, pp. 1031-32, 1035. Sjölander I indicates that these results confirm previous results regarding intraperitoneal immunization and suggest that retention of antigen at the injection site is not a feature of the immune potentiating properties of iscoms. Sjölander I, pp. 1035.

7. The fact that side effects in the form of local reactions were known to be most common with adjuvants that are not cleared rapidly from sites of injection is suggested, for example, by the Morein '354 patent, in view of Sjölander I and another reference to Sjölander, 43 Scand. J. Immunol. 164 (1996) (hereinafter "Sjölander II"), which is also submitted herewith. Specifically, as indicated above, the Morein '354 patent discusses the undesirable side effects associated with

conventional adjuvants, i.e. granulomas at the injection site associated with use of Freund's complete adjuvant or aluminium hydroxide, col. 1, lines 26-32. Sjölander I disclosed that release of radioactivity from the injection site after subcutaneous administration of ^{125}I-labeled flu-ag, i.e. radiolabeled influenza antigen, emulsified in Freund's complete adjuvant was slow, resulting in lower total recovery from blood and organs and retention of radioactivity at the site of injection for the whole experimental period. Sjölander I, p. 1032. Sjölander II disclosed that retention of antigen at the site of injection had also been observed for alum. Sjölander II, p. 170. Taken together, these disclosures would have suggested that side effects in the form of local reactions may be caused by retention of adjuvants at sites of rejection, and thus that an absence of iscom-triggered side effects in the form of local reactions likely reflects rapid clearance of iscom particles from sites of injection, not a lack of intensity of iscom-triggered inflammatory responses.

8. For at least the reasons above, it is my opinion that a person of ordinary skill would not have understood an absence of side effects in the form of local reactions in hosts to imply that live micro-organisms could likely survive long enough in the hosts to stimulate long-lived specific immunity. Rather, the person of ordinary skill would have understood the fact that iscom particles are cleared rapidly from sites of injection to explain the absence of such side effects despite intense inflammatory responses induced by iscom particles. Accordingly, for these reasons as well as the reasons previously presented in the Amendment dated November 6, 2009, it is my opinion that the person of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claimed compositions or methods.

9. I also understand that the reference to Van Woensel (U.S. Pat. No. 5,925,359) remains at issue in this case, in part based on the Examiner's assertion that none of the evidence presented specifically provides any teaching away from the combination of an iscom with a live vaccine. Contrary to the Examiner's assertion and in addition to the reasons previously presented, it is my opinion that the evidence presented specifically teaches away from the combination of an iscom with a live vaccine, for the following reasons.

10. It is well known in the art that (1) the immunostimulatory properties of adjuvants in general, and the proinflammatory properties of iscom particles in particular, result in inflammation in a host, (2) inflammation is directed, among other things, to rapid killing of live micro-organisms within the host prior to establishment of an infection by the live micro-organisms, and (3) establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires replication of the live micro-organism in the host in a controlled manner to give a subclinical infection stimulating long-lived specific immunity. Moreover, regarding inflammation in particular, it is also well known that susceptible live micro-organisms include attenuated-vaccine micro-organisms.

11. Independent support for the fact that the immunostimulatory properties of adjuvants in general, and the proinflammatory properties of iscom particles in particular, result in proinflammatory effects encompassing innate immunity and inflammation in a host is already of record in this case, as shown in the Amendment dated November 6, 2009, pp. 17-18, and the evidence cited therein, Smith I, p. 5536. Regarding the proinflammatory properties of iscom particles in particular, Smith discusses a potential role of IL-12 in

establishing the proinflammatory cascade associated with injection of iscom particles, p. 5536, and indicates that iscom particles stimulated the production of a wide range of inflammatory mediators, including the pro-inflammatory cytokines IL-1 and IL-6, p. 5543.

12. Independent support for the fact that inflammation is directed, among other things, to rapid killing of live micro-organisms within the host prior to establishment of an infection by the live micro-organisms is shown, for example, in Janeway et al., Immunobiology (2001), Chapter 1, pp. 1-2, and in Janeway, Chapter 2, pp. 37, 41, and 43, both of which are submitted herewith. For reference, Janeway's Immunobiology is well known as an authoritative textbook and source of information in the art.

13. Independent support for the fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires replication of the live micro-organism in the host in a controlled manner to give a subclinical infection stimulating long-lived specific immunity is shown, for example, in Janeway, Chapter 14, p. 583, and Janeway, Afterward, pp. 605-06, which are submitted herewith. Additional support is also already of record in this case. The additional support includes the Morein Declaration dated May 18, 2009, at para. 7, and the Fohlman Declaration dated June 15, 2009, at para. 8, both of which explain that live micro-organisms of live attenuated vaccines stimulate long-lived specific immunity based on replicating in a controlled matter to give a subclinical infection. The additional support also includes the Nobivac Tricat Data Sheet, http://www.intervet.co.uk/Products_Public/Nobivac_Tricat/090_product_Datasheet.asp, corresponding to Exhibit A of the Declaration of Morein dated November 4, 2009, which highlights the susceptibility of live attenuated viruses to being killed

and thus the importance of viability of the live attenuated viruses for their effectiveness regarding vaccination.

14. One of ordinary skill would have reasoned from these facts that developments flowing therefrom would have been unlikely to produce the objective of the Applicants' invention, or any other desirable objective. Specifically, one of ordinary skill considering the above-noted facts that the immunostimulatory properties of adjuvants in general, and iscom particles in particular, result in inflammation, including proinflammatory effects in a host, and that inflammation is directed, among other things, to rapid killing of live micro-organisms, including attenuated-vaccine micro-organisms, within the host prior to establishment of an infection by the live micro-organisms, would have reasoned that combining an adjuvant in general, and an iscom in particular, with a live micro-organism for use as a vaccine would likely have resulted in deleterious effects to the live micro-organism <u>following</u> administration to a host. One of ordinary skill considering the additional above-noted fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires replication of the live micro-organism in the host in a controlled manner to give a subclinical infection stimulating long-lived specific immunity would have reasoned that the likely deleterious effects of the resulting inflammation on the live micro-organism within the host would have made it unlikely that the live micro-organism could establish the subclinical infection required for development of long-lived specific immunity against the live micro-organism.

15. In addition to the reasons above, one of ordinary skill would have given Van Woensel no weight with regard to any suggestion that it may otherwise make regarding use of iscoms with live vaccines because Van Woensel expressly states

that saponins, vitamin E acetate solubilisate, and mineral oil emulsion such as Bayol and Marcol 52 are suitable adjuvants for use with Van Woensel's live attenuated vaccine, without apparently providing any experimental support, and one of ordinary skill would have found such a statement implausible absent experimental support.

16. One of ordinary skill would have found the statement regarding saponins implausible, particularly given the lack of experimental support, based on arguments and evidence that is already of record in the present case. See for example the Amendment dated November 6, 2009, pp. 12-13, and evidence cited therein.

17. One of ordinary skill would have found the statement regarding vitamin E acetate solubilisate and mineral oil emulsion such as Bayol and Marcol 52 implausible, particularly given the lack of experimental support, for at least the reason that Van Woensel expressly refers to these materials as solubilisate or mineral oil emulsion, and one of ordinary skill would have readily recognized that solubilisates and mineral oil emulsions are incompatible with live micro-organisms. Indeed, one of ordinary skill would have recognized that each of the emulsifiers disclosed by Van Woensel, i.e. Tween and Span, and each of the specific adjuvants disclosed by Van Woensel in addition to saponins, i.e. vitamin E acetate solubilisate, aluminium hydroxide, -phosphate or -oxide, and mineral oil emulsion such as Bayol and Marcol 52, would have been deleterious to live micro-organisms in a live vaccine and thus one of ordinary skill would have understood these other emulsifiers and adjuvants to be inappropriate for use in live vaccines. Moreover, the emulsifiers disclosed by Van Woensel are all commonly used in adjuvant formulations, particularly oil-based emulsion (water-in-oil or oil-in-water) type of adjuvants, but the numerous

review articles published on adjuvants over the years do not mention such adjuvants in the context of live attenuated vaccines.

18. Also in addition to the reasons above, one of ordinary skill would have given Van Woensel no weight with regard to any suggestion that it may otherwise make regarding use of iscoms with live vaccines because Van Woensel states with apparent, though implausible, certainty that saponins, vitamin E acetate solubilisate, and mineral oil emulsion such as Bayol and Marcol 52 are "suitable" adjuvants for use with the live attenuated vaccine of Van Woensel, whereas Van Woensel qualifies any suggestion therein regarding use of iscoms by stating that incorporation of the antigens in iscoms is a "possible" way of adjuvation. The implausibility of the statements regarding saponins, vitamin E acetate solubilisate, and mineral oil emulsion such as Bayol and Marcol 52, coupled with the qualification of the statement regarding iscoms, would have cast terminal doubt on the plausibility of any of the teachings or suggestions that Van Woensel might otherwise make regarding use of iscoms with live vaccines.

19. I also understand that the Examiner has asserted that Applicants' argument that there would have been no reasonable expectation of success in the use of iscoms as adjuvants in the compositions as claimed was itself directed to potentially negative results in the host to whom the vaccine is to be administered and to the live vaccine included in the composition. Contrary to the Examiner's assertion, for the reasons previously presented, it is my opinion that the effect of iscom particles on a live micro-organism within a host would not have been predictable to any degree, and thus one of ordinary skill would not have had a reasonable expectation of success with regard to use of iscom particles with a live vaccine to establish long-lived specific immunity against the

live micro-organism of the live vaccine.

20. Results in this area of immunobiology are highly unpredictable and experimental data are required to explore this field.

21. In this regard, one of ordinary skill would not have had a reasonable expectation of success in view of expected (i) direct physical damage of the live microorganism upon mixing with saponin-containing iscom particles, (ii) immediate killing at the site of injection by cells and innate mechanisms triggered by the adjuvant effects of the iscom particles, and (iii) killing or replication-inhibition of microorganisms by proinflammatory/inflammatory mechanisms stimulated by the adjuvant effects of the iscom adjuvant.

22. Arguments and evidence regarding the direct physical damage is already of record in the case, as shown in the Amendment dated November 6, 2009, pp. 12-13, and the evidence cited therein.

23. Independent support regarding the immediate killing at the site of injection is shown for example in Janeway et al., Immunobiology (2001), Chapter 1, pp. 1-2 (discussing phagocytic cells, which "are immediately available to combat a wide range of pathogens without requiring prior exposure and are a key component of the innate immune system"), and in Janeway, Chapter 2, pp. 36-37 ("[M]ost of the microorganisms that do succeed in crossing the epithelial surfaces are efficiently removed by innate immune mechanisms that function in the underlying tissues. Thus in most cases these defenses . . . prevent a site of infection from being established."), and 43 (see Summary paragraph).

24. Regarding the proinflammatory/inflammatory mechanisms stimulated by the adjuvant effects of the iscom adjuvant, the

bases for multiple inflammatory responses to iscom particles were not understood in the art. Consistent with this fact, Janeway, Afterward, pp. 608, states with regard to future directions of research in immunobiology that "[o]ne of the big questions is whether immunologists can figure out a way to really understand innate immunity, given that it is a system in which there is really no specific product to measure," and that "when one moves from experiments that test the functioning of the adaptive immune system to those that test the innate immune system, one is at a loss for proper controls."

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the present application or any patent issued thereon.

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